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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,003	04/28/2005	Helene Margaret Finney	CELL-0296	1691

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,003	FINNEY ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8-12,16-19,21,25,26,28,30 and 35-37* is/are pending in the application.

4a) Of the above claim(s) *10,16,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,9,11,12,17-19,21,25,26,28,30 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/533,003 filed on April 28, 2005 is a 371 of PCT/GB03/04639 filed on 10/28/2003. Relevant foreign application includes United Kingdom 0225279.9 filed on 10/30/2002.

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1, 2, 6, 8-12, 16-19, 21, 25, 26, 28, 30 and 37, drawn to nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from CD134 or the human inducible co-stimulator, and a composition comprising a nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from CD134 or the human inducible co-stimulator, and a composition comprising the nucleic and a pharmaceutically acceptable excipient, in the reply filed on Nov. 17, 2006 is acknowledged. The traversal is on the ground(s) that the technical feature that links groups I and II does, in fact, define a contribution over the prior art. Specifically, the applicants stated that "In contrast to the Office's assertion, the technical feature that links groups I and II is not a cytoplasmic signaling sequence derived from CD134 or the human inducible co-stimulator (ICOS), but, rather, is ***a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences***, at least one of which is derived from CD 134 or the human inducible co-stimulator". The traversal is not found persuasive because, upon further consideration, it is noted that Roberts

(PCT/US96/01293, WO 96/23814, listed in the IDS filed by applicants) teach novel co-stimulatory receptor chimeric DNA sequences, expression cassettes and vectors containing these sequences, as well as cells containing the chimeric DNA and novel chimeric receptor proteins expressed from the sequences, are provided where the novel co-stimulatory chimeric DNA sequences comprise three domains which do not naturally exist together: (i) ***at least one cytoplasmic domain***, *which normally transduces a co-stimulatory signal resulting in activation of a messenger system*, (2) at least one transmembrane domain, which crosses the outer cellular membrane, and (3) at least one extracellular receptor domain which serves to bind to a ligand and transmit a signal to the cytoplasmic domain, resulting in a co-stimulatory signal in the host cell in which the chimeric DNA is expressed. *Particularly, cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors are employed joined to other than their natural extracellular domain by a transmembrane domain.*

It is noted that the broadest and reasonable interpretation of the phrase "*at least one of the cytoplasmic signaling sequences is* ***derived from*** *the human inducible co-stimulator*" recited in claim 1 of instant application encompasses the cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors, taught by Roberts (1996) (See further elaboration in the rejection under 35 U.S.C. 102(b)).

With regard to requirement for election of species for cytoplasmic signaling sequences derived from either CD134 or the human inducible co-stimulator (ICOS), the applicant elects human inducible co-stimulator for prosecution. Accordingly, claims **10** and **16** reciting cytoplasmic signaling sequences derived from CD134 are withdrawn from further consideration

pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants cancelled the claims 3-5, 7, 13-15, 20, 22-24, 27, 29, and 31-34.

The requirement is still deemed proper and is therefore made FINAL.

Status of claims: 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37are currently under examination.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al., (Roberts et al., PCT/US96/01293, WO 96/23814, listed in IDS filed by the applicants).

It is noted that the broadest and reasonable interpretation of the phrase "cytoplasmic signaling sequences derived from the human inducible co-stimulator" recited in claim 1 encompass any polypeptide comprising any amino acid residue with cytoplasmic signaling function. The specification does not provide any correlation between structure and function of cytoplasmic signaling sequences, thereby, the interpretation is consistent with the statements in

the specification: "derivative" or "variant" mean any species variant or any variant comprising one or more amino acid substitution, deletion or addition, provided that the derivative or variant retains substantially the same functional capability as the original parent sequence. (See paragraph [0018] of instant application). *Therefore, based on this interpretation, any nucleic acid molecule encoding at least two cytoplasmic signaling molecules would anticipate the claimed nucleic acid molecules.*

Roberts (PCT/US96/01293, WO 96/23814, listed in the IDS filed by applicants) teach novel co- stimulatory receptor chimeric DNA sequences, expression cassettes and vectors containing these sequences, as well as cells containing the chimeric DNA and novel chimeric receptor proteins expressed from the sequences, are provided where the novel co-stimulatory chimeric DNA sequences comprise three domains which do not naturally exist together: (i) ***at least one cytoplasmic domain, which normally transduces a co-stimulatory signal resulting in activation of a messenger system***, (2) at least one transmembrane domain, which crosses the outer cellular membrane, and (3) at least one extracellular receptor domain which serves to bind to a ligand and transmit a signal to the cytoplasmic domain, resulting in a co-stimulatory signal in the host cell in which the chimeric DNA is expressed. ***Particularly, cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors are employed joined to other than their natural extracellular domain by a transmembrane domain.*** In this manner, host cells that express the chimeric co-stimulatory receptor protein can receive the necessary co-stimulatory signal by contact with the ligand as contrasted with the normal mode of activation of the cytoplasmic domain. *Additional embodiments of the co-stimulatory receptors include hybrid chimeric receptors, which contain*

both a cytoplasmic domain such as a ***CD3 chain of the TCR, for example zeta (i.e. TCRζ)****, as well as a cytoplasmic domain derived from a co-stimulatory molecule such as CD28, in a single chain to provide both a TCR activation signal and a co-stimulatory signal in the host cell* (See summary of the invention, bridging paragraph, pages 9-10, Roberts, 1996).

With regard to cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from human inducible co-stimulator (claims 1 and its dependent claims 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, and 30 of instant application), Roberts teaches novel chimeric co-stimulator receptor proteins and *DNA sequences encoding these proteins*. The chimeric receptors comprise at least three domains in a single chain molecule: an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic co-stimulation effector function signaling domain that acts synergistically with an effector function signal in the host cell. *Novel hybrid co-stimulatory receptor proteins include a second cytoplasmic effector function-signaling domain.* The invention further relates to expression cassettes containing the nucleic acids encoding the novel chimeric receptors, to *host cells* expressing the novel chimeric receptors and to methods of using the receptors to co-stimulate effector functions in the cells and for using cells expressing the receptors for treatment of cancer, disease and viral infections (See abstract, claims 11, 28, Roberts, PCT/US96/01293, WO 96/23814, listed in IDS filed by the applicants). More specifically, Roberts teaches chimeric cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4, CD2, or *CD3 chain of the TCR, for example zeta (i.e. TCRζ)* cell surface receptors are employed joined to other than their natural extracellular domain by a

transmembrane domain. (See bridging paragraph, pages 9-10, claims 12, 14, 30, 31, Fig. 1B, Roberts, PCT/US96/01293, WO 96/23814).

It is noted that the chimeric cytoplasmic signaling sequences comprising CD28, CTLA-4, CD2, and *CD3 chain of the TCR, for example zeta (i.e. TCRζ) taught by Roberts are considered as variants of the cytoplasmic signaling sequences derived from human inducible co-stimulator (ICOS) based on the claim interpretation mentioned in the beginning of this rejection.*

With regard to cytoplasmic signaling sequences derived from TCRζ (claim 11 of instant application), Roberts teach a cytoplasmic domain such as a CD3 chain of the TCR, for example zeta (i.e. TCRζ) (See summary of the invention, bridging paragraph, pages 9-10, and Fig. 1B, Roberts, 1996).

With regard to the extracellular ligand-binding domain being an antibody, or antigen-binding fragment (claim 21 of instant application), Roberts teaches the extracellular domain may be consist of monomeric or dimeric immunoglobulin (Ig) molecules (See lines 27-28, page 17, Roberts, PCT/US96/01293, WO 96/23814)

With regard to a vector (claim 25 of instant application) or a host cell comprising the recited nucleic acid molecule in claim 1 (claims 26, 28, and 30 of instant application), Roberts teaches a host cell being a lymphocytes (claims 33 and 42, Roberts) and various viral vectors to express chimeric co-stimulator receptor (See lines 7-10, page 26, Roberts, PCT/US96/01293, WO 96/23814). *It is noted that "A host cell" recited in claims 26 and 30 of instant application is interpreted as "An isolated host cell in vitro" based on the election of Group I, not Group II (which reads on a host cell in vivo).*

With regard to pharmaceutically acceptable excipient (claim 37 of instant application), Maher et al. teach inactive substances of a composition including calcium phosphate or DEAE-dextran mediated DNA transfection (lines 2-3, page 26, Roberts, PCT/US96/01293, WO 96/23814).

Thus, Roberts et al. clearly anticipates claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of instant invention.

4. Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Finney et al., (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002, listed in IDS filed by the applicants).

It is noted that the prior by Finney et al., (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002) is NOT an intervening art filed between the international filing date of instant application (PCT/GB03/04639 filed 10/28/2003) and the claimed foreign application (United Kingdom 0225279.9, filed on 10/30/2002). The prior art cited here by Finney et al. published on 04/25/2002, which was more than one year before the international filing date of instant application (PCT/GB03/04639 filed 10/28/2003).

Bearing the broadest and reasonable interpretation in mind (as mentioned in the proceeding 102(b) rejection anticipated by Roberts et al.), *any nucleic acid molecule encoding at least two cytoplasmic signaling molecules would anticipate the claimed nucleic acid molecules.*

Finney et al. (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002) teach nucleic acids are described which code for chimeric cytoplasmic signaling molecules containing at least one *cytoplasmic signaling sequence* derived from

CD137. The nucleic acids may be expressed in cells to produce *chimeric receptors* and other proteins, which are able to regulate cell activation processes with improved efficiency. Such regulated cells are of use in medicine, for example in the treatment of infectious, inflammatory and autoimmune diseases (See abstract, Finney et al., 2002).

With regard to the limitations of a nucleic acid molecule encodes at least two cytoplasmic signaling molecules (claim 1 and its dependent claims 2, 5, 9, 11, 12, 18, 21, 25, 26, 30, 37 of instant application) and three cytoplasmic signaling molecules (claim 8 and its dependent claims 17 of instant application), Finney et al. teach a nucleic acid encoding a cytoplasmic signaling molecule comprising at least two cytoplasmic signaling sequences, wherein at least one cytoplasmic signaling sequence is derived from CD137 (claim 1, Finney et al., 2002); nucleic acid according to claim 1, wherein at least one cytoplasmic signaling sequence is a primary cytoplasmic signaling sequence (claim 2, Finney et al., 2002); and a nucleic acid according to any one of claims 2 to 7, which encodes three cytoplasmic signaling sequences (claim 8, Finney et al., 2002).

With regard to a nucleic acid molecule encoding a chimeric receptor protein, which comprises an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a single cytoplasmic signaling sequence derived from the human inducible co-stimulator (claim 19 of instant application), Finney et al. teach A nucleic acid encoding a chimeric receptor protein, which comprises an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain is encoded by a nucleic acid according to any one of claims 1 to 14 (claim 15, Finney et al., 2002).

With regard to a vector and a host cell (claims 25, 26, 30 of instant application), Finney et al., teaches a vector for comprising a nucleic acid according to any of the proceeding claims (claims 20, Finney et al., 2002), and a host containing the nucleic acid expressing the peptide (claims 21, and 24, Finney et al., 2002).

With regard to a composition comprising a nucleic acid molecule according to claim 1 in conjunction with a pharmaceutically acceptable excipient (claim 37 of instant application), Finney et al., teach a composition comprising a peptide or polypeptide according to claim 22, a chimeric receptor protein according to claim 23, a nucleic acid according to any one of claims 1 to 19, or a vector according to claim 20, in conjunction with a pharmaceutically acceptable excipient (claim 27, Finney et al., 2002).

Thus, Finney et al. clearly anticipates claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of instant invention.

5. Claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Maher et al., (Maher et al., Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor. *Nat Biotechnol.* 20(1): 70-5, Jan. 2002; listed in the IDS filed by the applicants) as evidenced by Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants).

Bearing the broadest and reasonable interpretation in mind (as mentioned in the proceeding 102(b) rejections), with regard to cytoplasmic signaling molecule that comprising at

least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from human inducible co-stimulator (claims 1 and its dependent claims 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, and 30 of instant application), Maher et al. teach a recombinant chimeric TCRζ/CD28 receptor bearing hybrid TCRζ/CD28 cytoplasmic signaling domain, expressed from retroviral vectors (See Title, Fig. 1 [CD3ζ diagramed in **P28Z** construct is a TCR, T cell receptor], and Recombinant receptors and retroviral vector, Experimental protocol, page 74, Maher et al, 2002).

With regard to chimeric receptor protein comprising an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic signaling domain (claims 18, 19 of instant application), and the extracellular ligand-binding domain being an antibody, or an antigen-binding fragment (claim 21 of instant application), Maher et al. teach chimeric TCRζ/CD28 receptor comprising scFv coupled through human CD8α hinge and transmembrane sequences to the intracellular domain of human TCRζ (See Fig. 1, page 71, and Experimental protocol, page 74, Maher et al, 2002).

With regard to a vector (claim 25 of instant application) or a host cell comprising the recited nucleic acid molecule in claim 1 (claims 26, 28, and 30 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells --- Peripheral blood mononuclear cells from healthy donors (See Experimental protocol, page 75, Maher et al, 2002). *It is noted that "A host cell" recited in claims 26 and 30 of instant application is interpreted as "An isolated host cell in vitro" based on the election of Group I, not Group II (which reads on a host cell in vivo).*

With regard to acceptable excipient (claim 37 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells (See Experimental protocol, page 75, Maher et al, 2002), and thereby any inactive substance, other than the nucleic acid sequences encompassed by the retroviral vector, is considered as acceptable excipient, which includes water.

The cytoplasmic signaling sequences of involved in T-cell activation sharing related structures and functions is a known in the art (claim 1 of instant application) as evidenced by Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants). More specifically, Hutloff et al. teach the related functions of CD28 and ICOS in T cell activation and the amino acid sequences alignment between human ICOS and CD28, which demonstrated conserved amino acid throughout ICOS and CD28 sequences including C-terminal cytoplasmic signaling domain 166-199 of ICOS (See Fig. 1d, Hutloff et al., 1999).

Thus, Maher et al. clearly anticipates claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of the instant invention.

Conclusion

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600